International Journal of Women's Dermatology 2 (2016) 53–55

Contents lists available at ScienceDirect

International Journal of Women's Dermatology

Original Research

Evaluation of prolactin levels in patients with newly diagnosed pemphigus vulgaris and its correlation with pemphigus disease area index

Vahideh Lajevardi, MD [a,b], Zahra Hallaji, MD [a,b], Maryam Daneshpazhooh, MD [a,b], Narges Ghandi, MD [a,b], Peyman Shekari, MD [a], Sepideh Khani, MD [a,b,*]

[a] Department of Dermatology, Tehran University of Medical Sciences, Tehran, Iran
[b] Autoimmune Bullous Diseases Research Center, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article history:
Received 17 November 2015
Received in revised form 13 February 2016
Accepted 29 February 2016

Keywords:
autoimmunity
pemphigus vulgaris
prolactin

ABSTRACT

Background: Prolactin is a hormone; in addition to it known roles, it has immunomodulatory effects on lymphocytes maturation and immunoglobulins production. Hyperprolactinemia has been demonstrated in various autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, type I diabetes mellitus, and Graves' disease. In view of the prolactin immunomodulatory roles, studying prolactin levels in pemphigus as an autoimmune blistering disease may introduce new ways of understanding disease etiology and developing treatment strategies.
Objective: Our purpose was to determine the prolactin levels in patients with newly diagnosed pemphigus vulgaris and study its correlation with pemphigus disease area index.
Limitation: Our study was limited by the lack of a control group.
Methods: In this cross-sectional study, prolactin and anti-desmoglein 1 and 3 autoantibodies levels were measured in 50 patients with newly diagnosed pemphigus vulgaris in Razi Dermatology Hospital. Pemphigus severity and extent was estimated using the Pemphigus Disease Area Index.
Results: Of the 50 patients, 18 were male and 32 were female with a mean age of 41.56 ± 13.66 years. Mean prolactin (PRL) level was 15.60 ± 11.72 ng/ml (10.68 in males and 18.37 in females). Mean anti-desmoglein 1 and 3 autoantibodies were 135.8 ± 119.8 and 245.8 ± 157.4 U/ml, respectively. Eleven out of 50 patients had a higher than normal prolactin range. No relation was found between prolactin level and disease activity ($p = .982$). Also, correlation studies show no relation between prolactin and anti-desmoglein 1 and 3 autoantibodies levels (respectively, $p = .771$ and .738). In comparing the extent of the disease between the two groups with normal and high prolactin, paired t-test showed no significance ($p = .204$).
Conclusion: In our study, 22% of patients had hyperprolactinemia, which was greater among females. The highest PRL level was detected in mucocutaneous group. Although serum PRL levels were higher in patients with a greater Pemphigus Disease Area Index, it did not reach statistical significance.

Introduction

Prolactin (PRL) is a hormone mainly secreted from the anterior pituitary under the inhibition of dopamine and involved in lactogenesis. PRL is also produced in other sites, such as cells of the immune system. In addition to production by immune cells, prolactin has receptors on monocytes, macrophages, natural killer cells, and T and mainly B lymphocytes. In the last decades, studies have shown immunomodulatory effects of PRL on lymphocyte maturation and immunoglobulin production (De Bellis et al., 2005; Draca, 1995; Ignacak et al., 2012; Jara et al., 2011; Orbach and Shoenfeld, 2007; Shelly et al., 2012; Vera-Lastra et al., 2002).

Hyperprolactinemia has been demonstrated in autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, type I diabetes mellitus, Graves' disease, and multiple sclerosis (De Bellis et al., 2005; Draca, 1995; Ignacak et al., 2012; Jara et al., 2011; Moshirzadeh et al., 2012; Orbach and Shoenfeld, 2007; Shelly et al., 2012; Vera-Lastra et al., 2002). Some correlation has been described between lupus activity and PRL levels (Rezaieyazdi and Hesamifard,

* Corresponding author.
E-mail address: drsepidehkhani@gmail.com (S. Khani).

http://dx.doi.org/10.1016/j.ijwd.2016.02.004

2006). Furthermore, bromocriptine treatment as a dopaminergic agonist has been effective for some autoimmune diseases (Alvarez-Nemegyei et al., 1998; McMurray, 2001).

Pemphigus is a group of autoimmune blistering diseases, in which functional inhibition of desmoglein (Dsg) 1 and 3 by autoantibodies results in loss of cell-cell adhesion.

Despite vast research on pathophysiology of pemphigus, the exact causes of autoantibodies are unknown.

Khandpur and Reddy (2002) reported a case of new onset pemphigus vulgaris (PV) and idiopathic hyperprolactinemia that was responsive to steroid and bromocriptine treatment. Other studies have shown a correlation between PRL level and PV (Barzegari et al., 2004; Fallahzadeh et al., 2010; Helmy et al., 2013; Kavala et al., 2006).

In view of the prolactin immunomodulatory roles, further studies of prolactin levels in a pemphigus patient and its correlation with disease severity may introduce new ways of understanding disease etiology and developing treatment strategies.

Method and materials

All new patients diagnosed with PV in Autoimmune Bullous Diseases Research Center, Razi Hospital, Tehran University of Medical Sciences, Iran, between 2011 and 2012 were included in this case series. PV diagnosis was made by both pathologic and immunofluorescence studies.

Pregnancy or lactation; presence of renal, hepatic, or chest wall disease; recent abortion; taking antipsychotic or estrogen containing drugs; and use of opioids were exclusion criteria for this study.

Blood samples were collected before starting corticosteroid therapy and stored in laboratory at −70 °C. After collection completion, PRL levels were measured in the samples by chemiluminescence immunoassay (Cobas kits, Elecsys device). Anti-Dsg 1 and 3 autoantibodies levels were also measured in all patients as another disease activity index by enzyme-linked immunosorbent assay.

We used Pemphigus Disease Area Index (PDAI) as a measurement index of disease activity, which has 3 components relating to the skin, scalp, and mucous membranes. Activity score is a value given to the number of erosions, blisters, or new erythema at the time of examination. The maximum total score is 263, consisting of 250 points for the activity and 13 for damage scores (Daniel et al., 2012).

All data were analyzed using the Statistical Package for Social Sciences software (SPSS, Chicago, IL, version 20). The correlation between prolactin levels and the extent of involvement was studied by a Spearman test. A t-test was used to compare the extent of involvement in groups with normal and high PRL levels.

Results

Fifty patients were included in the study: 18 were male and 32 were female with a mean age of 41.56 (±13.66) years. Mean PRL level was 15.60 ± 11.72 ng/ml (10.68 in males and 18.37 in females).

Table 1
PRL levels among age groups.

Age Groups (years old)	No. of Patients	Prolactin Levels ng/ml (Mean ± SD)	Hyperprolactinemia PRL levels>23.3 ng/ml for Females PRL levels>15.2 ng/ml for Males
10-20	4	19.58 ± 14.86	2 (50%)
20-30	5	16.97 ± 10.78	2 (40%)
30-40	13	17.63 ± 18.51	3 (23.1%)
40-50	16	13.15 ± 6.91	1 (6.3%)
50-60	8	15.95 ± 8.34	2 (25%)
60-70	2	14.79 ± 1.03	1 (50%)
70-80	2	10.09 ± 2.22	0
Total	50	15.60 ± 11.72	11 (22%)

Table 2
PRL levels among PV subtypes.

Pemphigus Type	No. of Patients	Prolactin Levels ng/ml (Mean ± SD)	Hyperprolactinemia PRL levels>23.3 ng/ml for Females PRL levels>15.2 ng/ml for Males
Mucocutaneous	31	15.77 ± 11.25	9
Mucuosal	11	17.62 ± 16.48	1
Cutaneous	8	12.18 ± 3.43	1

To study PRL levels according to age, patients were divided into seven age groups. Eleven out of 50 patients (eight females and three males) had PRL higher than normal (Table 1). Thirty-one patients had mucocutaneous, 11 patients had only mucuosal, and eight patients had only cutaneous as the site of involvement (Table 2).

Mean anti-Dsg 1 and 3 autoantibodies levels were 135.8 ± 119.8 and 245.8 ± 157.4 U/ml, respectively (laboratory range: negative ≤14 and positive ≥ 20). Based on PDAI, mean index was 19.76 ± 14.07 with a range of 3 to 63.

No relation was found between PRL level and disease activity by Spearman test, neither totally ($p = .982$) nor among gender groups separately with $p = .582$ for female group and .592 for male group.

The average extent of involvement in the group with high PRL was 25.72, 18.07 in the group with normal PRL. Paired t-test showed no significant difference in disease extent between patients with normal PRL and those with high PRL ($p = .204$).

The mean extent of involvement among men with high and normal PRL were 20.33 and 20.55, respectively. Women showed a mean extent of 27.75 in the group with high PRL levels and 16.54 in the group with normal levels of PRL. Similarly, paired t-test with $p = .997$ among men and .175 among women did not show any significant association.

No significant relation was found between PRL level and cutaneous, mucosal, or mucocutaneous subtypes; p values were 0.247, 0.904, and 0.601, respectively.

Anti-Dsg 3 levels had significant correlation with PDAI ($p = .01$). Anti-Dsg 1 and 3 levels correlation with PRL levels were nonsignificant ($p = .771$ and .738, respectively).

Kolmogorov–Smirnov test was applied to study the distribution of the extent of involvement and was normal.

Discussion

In the past 2 decades, studies have revealed extrapituitary sources of PRL as well as its immunoregulatory role.

Hyperprolactinemia has been observed in some autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, type I diabetes mellitus, and Graves' thyroiditis. Vesiculobullous skin diseases, like the pemphigus group, have an autoimmune etiology.

Research has been conducted on hyperprolactinemia prevalence and its correlation with disease activity in patients with pemphigus. Barzegar et al.'s (2004) study of 44 patients with autoimmune blistering skin disease showed significantly higher prolactin levels in comparison to control group. Kavala et al. (2006) reported significantly increasing PRL levels during active phases of the disease compared to the control group in both male and female patients ($p < .05$ and $< .01$).

Helmy et al.'s (2013) study from Egypt showed no statistically significant difference between serum PRL levels in PV patients and controls. The highest serum PRL level was detected in patients with mucocutaneous involvement, followed by those with mucosal involvement, and was the least in those with cutaneous involvement. However, there was no statistically significant difference among the three types. A highly significant correlation was found between PRL level and the extent of body surface involvement.

In a cross-sectional study by Fallahzadeh et al. in 2010, mean PRL levels of PV patients were significantly higher than those in the control group ($p = .048$), and there was a positive correlation between serum prolactin levels and extent of disease (Fallahzadeh et al., 2010).

Some animal and human studies show stress-induced prolactin rise (Noel et al, 1972; Schedlowski et al, 1992; Seggie and Brown, 1975). On the other hand, quality of life studies on blistering diseases describe impairments and psychological distress among pemphigus patients (Ghodsi et al, 2012).

In our study, 22% of patients had hyperprolactinemia, which was greater among females. The highest PRL level was detected in the mucocutaneous group, followed by the cutaneous and then the mucosal groups. Comparison among these three groups showed no significance, which is in concordance with the results of Helmy et al.'s (2013) study.

Although we could not find statistically significant correlation between PRL level and disease activity, serum PRL levels were higher in patients with greater PDAI. That may be explained by the PRL and immune system relations. Nevertheless, a stress induced increase in PRL levels might be a confounding factor.

In this study, PRL was measured only in new patients before starting therapy with corticosteroids or immunomodulatory medications. Further studies can be done on changes on PRL level with disease progression and/or after treatment.

PRL levels were measured before starting of steroids and immunomodulatory drugs.

Literature reviews demonstrate the immunomodulatory effect of PRL, and further studies need to stabilize PRL levels screening values as a prognostic factor.

Conclusion

In our study, higher than normal serum prolactin levels were detected in patients with greater PDAI. Although it did not reach statistical significance, its consistency with other studies can further demonstrate PRL immunomodulatory effects.

Acknowledgements

This research was supported by Tehran University of Medical Sciences and Health Services.

References

Alvarez-Nemegyei J, Cobarrubias-Cobos A, Escalante-Triay F, Sosa-Munoz J, Miranda JM, Jara LJ. Bromocriptine in systemic lupus erythematosus: a double-blind, randomized, placebo-controlled study. Lupus 1998;7(6):414–9.
Barzegari M, Shams Davachi SH, Kianfar A. Evaluation of serum prolactin levels in patients with autoimmune blistering skin diseases: a case-control study. Iran J Dermatol 2004;7:261–3.
Daniel BS, Hertl M, Werth VP, Eming R, Murrell DF. Severity score indexes for blistering diseases. Clin Dermatol 2012;30:108–13.
De Bellis A, Bizzarro A, Pivonello R, Lombardi G, Bellastella A. Prolactin and autoimmunity. Pituitary 2005;8(1):25–30.
Draca S. Prolactin as an immunoreactive agent. Immunol Cell Biol 1995;73(6):481–3.
Fallahzadeh MK, Lashkarizadeh H, Kamali-Sarvestani E, Namazi MR. Elevation of serum prolactin levels in patients with pemphigus vulgaris: a novel finding with practical implications. J Am Acad Dermatol 2010;62(6):1071–2.
Ghodsi SZ, Chams-Davatchi C, Daneshpazhooh M, Valikhani M, Esmaili N. Quality of life and psychological status of patients with pemphigus vulgaris using Dermatology Life Quality Index and General Health Questionnaires. J Dermatol 2012;39(2):141–4.
Helmy A, Azab M, El-Kader MA, Nassar A, Embaby H. Role of prolactin in pemphigus vulgaris. Egypt J Dermatol Venerol 2013;33:12–7.
Ignacak A, Kasztelnik M, Sliwa T, Korbut RA, Rajda K, Guzik TJ. Prolactin—not only lactotrophin. A "new" view of the "old" hormone. J Physiol Pharmacol 2012;63(5):435–43.
Jara LJ, Medina G, Saavedra MA, Vera-Lastra O, Navarro C. Prolactin and autoimmunity. Clin Rev Allergy Immunol 2011;40(1):50–9.
Kavala M, Sarıgül S, Kocatürk Ö. Emek. Pemfigus Hastalarinda Serum Prolaktin Düzeyleri. Türkderm 2006;40:52–5.
Khandpur S, Reddy BS. An unusual association of pemphigus vulgaris with hyperprolactinemia. Int J Dermatol 2002;41(10):696–9.
McMurray RW. Bromocriptine in rheumatic and autoimmune diseases. Semin Arthritis Rheum 2001;31:21–32.
Moshirzadeh S, Ghareghozli K, Harandi AA, Pakdaman H. Serum prolactin level in patients with relapsing-remitting multiple sclerosis during relapse. J Clin Neurosci 2012;19(4):622–3.
Noel GL, Suh HK, Stone JG, Frantz AG. Human prolactin and growth hormone release during surgery and other conditions of stress. J Clin Endocrinol Metab 1972;35(6):840–51.
Orbach H, Shoenfeld Y. Hyperprolactinemia and autoimmune diseases. Autoimmun Rev 2007;6(8):537–42.
Rezaieyazdi Z, Hesamifard A. Correlation between serum prolactin levels and lupus activity. Rheumatol Int 2006;26:1036–9.
Schedlowski M, Wiechert D, Wagner TO, Tewes U. Acute psychological stress increases plasma levels of cortisol, prolactin and TSH. Life Sci 1992;50(17):1201–5.
Seggie JA, Brown GM. Stress response patterns of plasma corticosterone, prolactin, and growth hormone in the rat, following handling or exposure to novel environment. Can J Physiol Pharmacol 1975;53(4):629–37.
Shelly S, Boaz M, Orbach H. Prolactin and autoimmunity. Autoimmun Rev 2012;11(6-7):A465–70.
Vera-Lastra O, Jara LJ, Espinoza LR. Prolactin and autoimmunity. Autoimmun Rev 2002;1(6):360–4.